Cardiovascular and Renal Drugs Advisory Committee Meeting

July 29, 2009

Questions to the committee

Questions 1.1. and 1.2.

1.1. In comparing a new treatment to ramipril, is it sufficient to ensure that the new treatment would likely have been superior to placebo? On what endpoint?

1.2. If not, what proportion of this benefit is it appropriate to ensure has been preserved? On what endpoint?

Question 2

- In non-inferiority testing, there are various strategies intended to ensure that the new therapy would likely have been superior to placebo. How did the sponsor's strategy address …

2.1. use of a single reference study?

2.2. choice of end point from HOPE?

2.3. early termination of HOPE?

2.4. evolving treatment of high-risk patients?

Question 3 and 4

3. Are EUROPA (perindopril) and PEACE (trandolapril) relevant? If so, given the results of EUROPA and PEACE, …

   3.1. … how confident are you in the constancy assumption? What discount on the expected effect of ramipril is appropriate?

   3.2. … should a pooled analysis of ACE effect size be based upon fixed-effect or random-effect modeling?

4. What should the non-inferiority margin be?

Question 5

5. What role do the following observations play in your consideration of the effectiveness of telmisartan for reducing cardiovascular events?

5.1. The lack of superiority of the combination of telmisartan and ramipril to ramipril alone in ONTARGET (HR 0.99; 95% CI 0.92-1.07; p=0.85).

5.2. The lack of effect on the 4-component primary end point in TRANSCEND, a placebo-controlled study in high-risk ACE-intolerant patients (HR 0.92; 95% CI 0.81-1.05; p=0.22).

5.3 The favorable trend on the 3-component endpoint in TRANSCEND (HR 0.87; 95% CI 0.76-1.00; p=0.049).

5.4 The lack of effect seen in PRoFESS, a placebo-controlled study in patients with a prior stroke (HR 0.94[1]; 95% CI 0.83-1.01; p=0.11).

[1] This is for the 4-fold cardiovascular composite end point, not for the primary end point, which was stroke.

Questions 6

6a (vote) Should telmisartan be approved to reduce cardiovascular events in patients at high risk for such events?

6b (vote) If you voted no, should telmisartan be approved to reduce cardiovascular events in patients at high risk for such events and who can not tolerate ramipril

After voting, please comment on the rationale for your vote.